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Questions and Answers on Hormone Replacement Therapy

In Response to the Women's Health Initiative Study Results on Estrogen and Progestin Hormone Therapy

Many women have questions about whether to use or continue using hormone therapy (HRT) after the recent halting of the Women's Health Initiative (WHI) study on combined estrogen and progestin use in healthy postmenopausal women.

Experts from The American College of Obstetricians and Gynecologists (ACOG) have carefully reviewed the published study results. (To date, the complete WHI study data have not been released to outside organizations.) ACOG-member physicians have responded to questions from thousands of women around the country. Here ACOG addresses the most frequently asked questions about the published results of the WHI study and what they may mean for women facing decisions about HRT.

We hope the following information is helpful. Since it is not a substitute for medical advice, ACOG urges each reader to consult her personal physician when deciding about HRT.

Background on the WHI Study Results

The Women's Health Initiative is a long-term study sponsored by the National Institutes of Health (NIH) that is looking at ways to prevent heart disease, breast and colon cancer, and osteoporosis.

One part of that study followed 16,608 healthy women with a uterus, who were ages 50 to 70 when they entered the study, and who took either estrogen and progestin therapy (combined hormone therapy, or HRT) or a placebo. The goal of this 8-year trial was to study the relationship between HRT and its possible benefits for heart disease and hip fracture, as well as its possible risks for breast cancer, endometrial cancer, and blood clots. The trial was not intended to study the effect of HRT on menopausal symptoms or on other conditions such as Alzheimer's disease.

On July 9, 2002, the NIH halted this trial after 5.2 years, concluding that the risks for the study group on combined HRT outweighed the benefits. (The published report is in the July 17, 2002 issue of the *Journal of the American Medical Association*. Additional information on the WHI can be found at the website www.whi.org.) Risks included small but significant increased risks of breast cancer, coronary heart disease, stroke, and blood clots for the group of women on HRT. Benefits of HRT use included lower risks for hip fractures and colon cancer. There was no difference between the two groups in death rates. A separate WHI trial on the use of estrogen alone (ERT) in women who have had a hysterectomy is continuing, because study officials have apparently not seen comparable risks in those women. The data and safety monitoring board of the WHI will continue to review data from this trial every six months.

The NIH is continuing to review a number of the statistics that were part of the WHI study, conducting what are known as subset analyses of the WHI data. So far, the NIH has issued its published *JAMA* report but has not released the underlying WHI data to outside organizations including ACOG. As the WHI data become available and as NIH announces the results of subset analyses, there may be further clarification of HRT issues and further revisions to ACOG recommendations.

YOUR QUESTIONS

1. What are the specific risks uncovered by the WHI study?

While there was no difference in the death rates between the group on HRT and the placebo group, there was a small but significant increased risk of certain diseases for the group of women on HRT. NIH officials concluded these risks were significantly high enough to justify stopping the study for public health reasons. These risks can be summarized as follows.

Heart Disease - Unlike earlier observational studies that suggested the possibility of some protection against heart disease, this study showed a small but significant increased risk for events such as non-fatal heart attacks. The risk for heart disease was 29% higher for the group taking combined HRT than for the group on placebo. While this percentage reflecting the increased risk for the group seems large, the annual increased risk for an individual woman was still relatively small. For example, on average during a year of the WHI study, there were 37 heart disease events (such as heart attacks) per 10,000 women in the HRT group compared to 30 events per 10,000 women in the placebo group. Thus there were, on average, 7 more cases per 10,000 women per year in the HRT group. The risk appeared in the first year of HRT use.

Breast Cancer - The risk for invasive breast cancer was 26% higher in the group on HRT. The annual increased risk for an individual woman was still relatively small. On average, per year there were 38 cases of breast cancer per 10,000 women on HRT compared to 30 breast cancer cases per 10,000 women on placebo. Thus there were, on average, 8 additional cases of breast cancer per 10,000 women per year, in the HRT group. The increase in breast cancer was apparent after 4 years of HRT use, and the risk appears to be cumulative, increasing over time. While the risk for breast cancer was also increasing for the placebo group over time -- because advancing age increases one's risk for breast cancer -- the risk for the HRT group appeared to increase at a higher rate than would normally occur with advancing age.

Stroke and Blood Clots - *Stroke*: There was a 41% increased risk for the group on HRT. On average, per year there were 29 cases of stroke per 10,000 women on HRT compared to 21 cases of stroke per 10,000 women on placebo (8 more cases per 10,000 women). The risk appeared in the second year of HRT use and continued into year 5 of the study. *Blood Clots*: The group on HRT had two-fold greater rates of blood clots than the group on placebo. On average, per year there were 34 cases of blood clots per 10,000 women on HRT compared to 16 cases per 10,000 women on placebo (18 more cases per 10,000 women).

2. Weren't there benefits or protections to HRT use as well?

Yes, but the study was stopped because these were not considered to be sufficiently strong enough to outweigh the increased risks for the group using HRT. These were the benefits shown:

Colon Cancer - The risk of colon cancer was reduced by 37% in the HRT group. On average, per year there were 10 cases of colorectal cancer per 10,000 women on HRT compared to 16 cases of colorectal cancer per 10,000 women on placebo (6 fewer cases per 10,000 women). The benefit appeared after 3 years of use and became more significant over time.

Bone Fractures - The WHI study was the first to show a decreased risk of vertebral and other osteoporotic fractures with HRT use. In the HRT group, there was a 24% reduction in total fractures, and a 34% reduction in hip fractures. On average, per year there were 10 cases of hip fracture per 10,000 women on HRT compared to 15 cases per 10,000 women on placebo (5 fewer cases per 10,000 women).

3. How do I apply these conflicting accounts of risk - whether "small" or "significant" -- to my own situation? If a study was halted, isn't HRT unsafe, period?

Knowing how to apply the risks uncovered by the WHI is complex for both patients and physicians. That's because there's a difference between the size of the risks found for the *group* of women using HRT, which were large enough to warrant stopping the study, and the size of the risks for each *individual woman* using HRT, which -- though real and often increasing over time -- were still quite small. A look at the breast cancer risk illustrates this difference, and some of the problems.

Risks for the Group on HRT: The NIH stopped the study for public health reasons, both in fairness to the group of women on HRT and because they were looking at the increased risks for an entire population of women using HRT over time. While the rate of increased breast cancer risk described in Question 1 may not sound huge (8 additional cases of breast cancer per 10,000 women, on average per year, in the HRT group), in a drug taken by millions of women over many years, this can result in a large number of women with breast cancer.

Risks for the Individual Woman on HRT: Since the percentage of women in the WHI study who actually had adverse effects from HRT use was small, the size of the risk for each individual woman on HRT was also small. For example, with breast cancer, while the increased risk for the group on HRT was 26%, an individual woman's increased risk for breast cancer with HRT use was *less than one tenth of one percent a year*, according to study authors. There's one important caveat however. This small increase in individual risk appeared to be *cumulative* over time. The longer a woman stayed on HRT, the more her risk for breast cancer increased, at a higher rate than would normally occur with advancing age.

What does this mean for a woman trying to make a decision about HRT? The bottom line is that while HRT is still an acceptable option for the treatment of menopausal symptoms in certain cases, the decision for a woman considering whether to use HRT and for how long has become much more complex.

> You will have to decide in consultation with your doctor whether the risks uncovered by the WHI are acceptable to you. This means reviewing with your doctor:
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> (1) why you want to be on HRT;
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> (2) your personal benefits with HRT use; and
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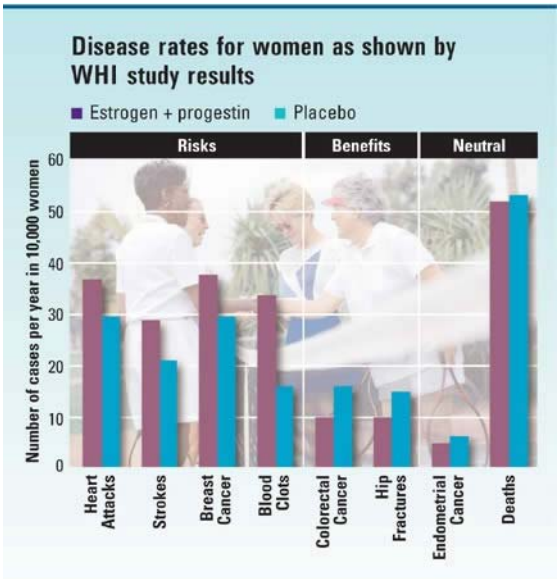
> (3) your increased risks with HRT use, taking into account your individual and family history for conditions such as heart disease or breast cancer.

ACOG recognizes that many women are tired of the phrase "talk to your doctor," which has been in constant use since the WHI report was published. But the phrase has never been more important. When it comes to HRT, there is no one-size-fits-all answer, and decisions about HRT will have to be made on a case-by-case (or woman-by-woman) basis.

The following chart may be helpful, which illustrates the differences in risks and benefits for the group on HRT as compared to the placebo group.



4. I was taking HRT for the reason that it could help prevent heart disease. Now the WHI says it doesn't. What happened?

HRT is no longer recommended to prevent heart disease in healthy women (primary prevention) or to protect women with pre-existing heart disease (secondary prevention). The WHI tells us that not only does it not work, it may actually increase your risk of a heart attack or stroke.

Why did medicine once think otherwise? Earlier observational studies compared women who took HRT with women who didn't. But these studies are not as sophisticated as the WHI study, which was "double-blinded" -- that is, it compared patients on HRT with a "control group" on placebo, with neither group knowing which pill they were taking. The earlier observational studies suggested that HRT had a benefit in protecting the heart, since the women on HRT had better cholesterol levels, and they appeared to have fewer heart attacks and strokes. In addition, these women may have been younger when they started HRT than the women in the WHI study.

Now, we are all benefiting from the effort in years past to increase the size and sophistication of research trials in women's health. The higher-quality WHI evidence suggests that these earlier studies probably had an inherent bias, meaning that the women taking HRT already tended to be healthier than the women not taking HRT. Also, there may be other, still-unknown factors that are affecting a woman's heart disease risk as much as, or more than, such known factors as cholesterol levels.

5. So, if I'm taking HRT just to protect against heart disease, should I stop?

Yes. Lifestyle changes can help prevent heart disease -- particularly regular exercise, smoking cessation, and weight control. And, for certain women at high risk for heart disease, other medications have been shown to be effective. Medications such as statins can help reduce high cholesterol levels, and hypertension medications can help reduce high blood pressure. You will want to discuss with your doctor the specific type that may be right for you.

6. I'm at high risk for osteoporosis. Can I continue on HRT?

If you are taking HRT *solely* for the prevention of osteoporosis consider stopping it, because there are other medications that can help prevent osteoporosis and fractures that appear to carry lower risks for conditions such as breast cancer or heart disease. If you are also taking HRT for treatment of menopausal symptoms, it may be appropriate. (See Question 7.)

Other preventive drug therapies include the family of drugs known as bisphosphonates, which can reduce the breakdown of bone. Other options are the selective estrogen receptor modulators, or SERMS, which are a new class of synthetic estrogens that act like estrogen in certain parts of the body (such as the bones) while leaving other parts of the body unaffected.

Some women with heartburn or ulcer problems may be unable to take bisphosponates, and each of the medications discussed here will have its own side effects. Although these medications appear to have a better ratio of benefits to risks for you compared to HRT, studies are continuing on the effects of these drugs, some of which have been in use for only a few years. Talk to your doctor about whether these medications would be appropriate for you. Weigh any benefits of continued HRT use against your personal risks for cardiovascular disease and breast cancer.

For all women, lifestyle recommendations for healthy bones include a diet high in calcium (postmenopausal women should be taking 1,200 to 1,500 mg of calcium per day), a multi-vitamin containing Vitamin D, and regular weight-bearing exercise such as jogging or walking.

7. Where does this leave me if I want to take HRT for menopausal symptoms such as hot flashes or sleep problems?

HRT is highly effective in treating certain menopausal symptoms and may still be appropriate for you, depending on your circumstances. However, the small but real increased risks uncovered by the WHI study mean that this is now a more complicated decision.

You will have to evaluate, with your physician, the pros and cons of HRT use in your individual circumstance. This includes weighing any benefits of continued HRT use against your individual risks for conditions such as breast cancer, to decide whether taking HRT is an acceptable or an unacceptable risk for you.

To date, HRT is the most effective treatment for the relief of vasomotor symptoms such as hot flashes and sleep disturbances, which can affect both physical and mental health. It's also effective in treating genitourinary symptoms such as urinary incontinence, or vaginal dryness, which can affect sexual pleasure.

The effects of these menopausal symptoms on the quality of a woman's life can be considerable, and the severity and duration of symptoms can vary widely from woman to woman. Some women experience few or very short-lived symptoms, while others experience severe symptoms over many years. Yet too often, women are made to feel guilty about how they respond to menopausal symptoms, which are often trivialized by such comments that women should simply be able to "put up with it." In fact, each woman will have her own physiological reaction to menopause, and each will have to make the decision that is right for her.

Some women may choose to manage their symptoms without any use of HRT, either through lifestyle changes alone or with other therapies. Other women, particularly those with severe menopausal symptoms, may conclude that the benefits of short-term HRT use are worth the small increased risks.

> If you choose HRT for relief of menopausal symptoms, ACOG recommends the following:
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> (1) Take HRT for the shortest possible time that works for you, in the smallest effective dose;
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> (2) Have regular consultations with your physician - at least once a year - to review your reasons for taking HRT and to see if you can successfully discontinue HRT use; and
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> (3) Like all women, get regular breast cancer screenings, including annual physician breast exams and periodic mammograms (which ACOG recommends every one to two years during your forties, and annually thereafter).

8. If I've been on HRT for more than 5 years for relief of menopausal symptoms, should I go off of it?

Try to discontinue HRT use if you have been on it for this period of time, since the increased risk of breast cancer and other conditions rises over time. If you do experience a return of symptoms, ask your doctor about alternative therapies. (See Question 14.)

What if you discontinue HRT after several years of use, but your menopausal symptoms come back and other therapies do not work for you? You can consider returning to HRT so long as you understand the risks involved. There are some women who will do better on HRT than on other therapies, and HRT may be a reasonable option for them if they have weighed the pros and cons with their physician. If you do resume HRT, do so at the lowest possible effective dose for you for the shortest possible time and, as discussed above, review with your physician at least annually whether you can successfully discontinue HRT.

9. Am I safe then if I take HRT for up to 4 years, since the increased risk for breast cancer appeared after that time?

We just don't know yet. There are no data from this or other studies to clearly establish what constitutes safe short-term use. Even the first 4 years of HRT use may not be risk free. In the WHI study, there was an increase in the *diagnosis* of breast cancer after 4 years. It's possible that hormones are having some effect on the biology of breast cancer even in the first year of use.

It's also possible that as the NIH conducts and releases further analyses of different parts of the WHI data, we may get a better picture of certain factors (such as a participant's prior use of HRT) to improve our understanding of why the increased breast cancer risk appeared when it did. Until we know more, if you do choose HRT, use it for the shortest possible time that works for you and have an evaluation with your physician at least annually to see whether you still need it.

10. I'm not taking the Prempro pill studied by the WHI, but another form of hormones. Do any of these results apply to me?

It's true that this part of the WHI only studied a specific combined estrogen and progestin pill and thus findings can be reasonably applied only to this formulation (which was .625 mg/d continuous conjugated equine estrogen and 2.5 mg/d medroxyprogesterone acetate; brand name Prempro™). However, we cannot assume other hormone regimens or methods will be safer, without more conclusive data. Although future studies on lower hormone doses or different combinations may tell us more, for now *all* women taking *all* forms of HRT should be aware of the increased risks found in the WHI trial.

11. I've had a hysterectomy and I'm taking estrogen alone. Is that still safe?

Another part of the WHI study that is examining the use of estrogen alone in women who have had a hysterectomy is continuing, because so far the same proportion of risks to benefits has not appeared in this group. Safety monitoring officials of the WHI will continue to review data from this part of the study every six months. However, complete results of this particular trial probably will not be known until the year 2005.

12. I haven't had a hysterectomy. Is it okay to switch to estrogen alone for the treatment of menopausal symptoms?

It is not recommended, since we know that women with a uterus who take only estrogen are at greater risk for endometrial cancer.

13. If I want to discontinue HRT use, what's the best way to do so -- "cold turkey" or gradually?

So far, there are no definitive studies to guide this process. You and your physician will have to discuss what method might work for you. Some women may tolerate "cold turkey," while others may require a more gradual approach. When stopping HRT, some women experience heavy vaginal bleeding. If menopausal symptoms recur with the abrupt approach, a gradual approach should be considered.

14. If I stop HRT and my menopausal symptoms return, what else can I try?

Some lifestyle modifications may help reduce symptoms such as hot flashes. These include quitting smoking; avoiding or reducing foods or substances that may trigger flashes, such as spicy foods, caffeine and alcohol; lowering stress levels; exercising regularly; and wearing loose clothing or dressing in layers, to peel off top layers during a hot flash.

There have been reports that some non-hormonal prescription medications may help relieve certain menopausal symptoms, although studies to date on these medications have been small and still lack long-term follow-up data. For example, for women experiencing vasomotor symptoms such as hot flashes and loss of sleep, the class of antidepressants known as selective serotonin reuptake inhibitors (SSRIs) may provide some relief. Clonidine, a type of anti-hypertension medication, may be helpful in some cases. Although these medications have been extensively studied and FDA approved for other uses, they have not yet been approved or marketed specifically for use in treating hot flashes. Talk to your physician about other possible medications for hot flashes.

For symptoms such as vaginal dryness, alternative delivery methods of estrogen alone -- such as vaginal creams, vaginal tablets, or vaginal rings -- are usually effective. Although the tablets and rings do not appreciably increase the estrogen levels in a woman's body, there are little data to assess the long-term safety of these three alternatives.

If you try other options and they do not relieve your symptoms, you can consider returning to HRT, as long as you understand the risks and benefits.

15. What about natural or herbal remedies such as black cohosh, for relief of symptoms? I have a friend on black cohosh who swears it works.

Some of the herbal preparations sold over-the-counter contain phytoestrogens, weak forms of estrogen derived from plants. Unfortunately, most nutritional supplements have not undergone long-term tests for safety and effectiveness, so no one really knows for sure how helpful they are and whether or not they might have any risks. Ongoing research may help shed some light on the subject, but most study results are still a number of years away. If you do use herbal remedies, always inform your physician of this as well as of any medications you take. [For more information on this topic, click here for ACOG Practice Bulletin #28, Use of Botanicals for Management of Menopausal Symptoms, June 2001.]

An Important Note: Research Continues, Recommendations May Change

If you have additional questions you would like to ask ACOG about HRT or other treatments for menopausal symptoms, email us at communications@acog.org.

Research on HRT and other therapies is continuing every day and medical recommendations may change. At present, the NIH is conducting further subset analyses of the WHI data. Despite requests to obtain them, the data have not yet been released to outside organizations. As these data become available, ACOG will update its recommendations accordingly.

Finally, remember that ACOG's statements here are for general informational purposes and should not be construed as medical advice. Before making a decision about HRT, consult with your physician for individualized advice that takes into account your personal needs and your medical and family history.

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ACOG is the national medical organization representing over 40,000 physicians who provide health care for women.